REMARKS

Claims 1-3, 6-10 and 13 have been rejected under 35 USC 102 over Fabbri in view of Samaritani, claims 1, 4, 5, 11 and 12 under 35 USC 103 over the same combination in further view of Fujioka and claims 1, 2 and 13-15 under 35 USC 103 over Fabbri, Samaritani and Tarantino. All of these rejections are respectfully traversed.

The present invention relates to a pharmaceutical composition which contains a solid intimate mixture of human growth releasing factor (GRF) and a stabilizing amount of saccharose or to a solution formed by reconstituting the solid mixture, and to a process of forming a lyophilizate. The claimed invention is not rendered obvious by the references applied in the outstanding Office Action.

The Fabbri patent relates to GRF. It does not, as recognized by the PTO, teach or suggest the use of saccharose in a GRF composition, or indeed any pharmaceutical composition, for any purpose. Indeed, there is no reference to stabilization in this patent although there is a reference to a composition containing mannitol as an excipient.

Fujioki has been cited to teach lyophilization of a composition containing 10mg/vial of GRF. It teaches that GRF is rather unstable and hardly preservable in a solution. It further teaches that lyophilization is not satisfactory because there is significant reduction in the titre when preserved at room temperature for a long period of time or exposed to heating, humidification or light as a result of the methionine at position 27 of the amino acids forming GRF being oxidized. Addition of antioxidants such as L-ascorbic acid had been unsatisfactory (col. 1, lines 36-48). The reference teaches that after strenuous efforts to overcome the problem, it was determined that human serum albumin or glycine can be used as a stabilizer. There is no teaching or suggestion in this reference that saccharose can be used as a effective stabilizer for GRF.

Quiet to the contrary, the reference implies that finding an effective stabilizer for GRF is quite difficult.

The newly cited Tarantino reference has been set forth to show compositions comprising a GRF buffer to a pH of 4. The reference relates to a composition for the sustained release of biologically active compounds which can be proteins or polypeptides including, inter alia, GRF. It indicates that the composition may contain stabilizers and specifically mentions human serum albumin, alpha-tocopherol and disodium EDTA. No particular stabilizer is associated with GRF and indeed the reference states "these stabilizing substances will differ depending on the particular active ingredient that will be incorporated into composition." Col. 3, lines 48-51. There is no teaching or suggestion of the use of saccharose as a stabilizer in this reference.

The background in the present application likewise acknowledges that GRF requires stabilization. It points out that the available literature teaches that GRF suffers from chemical degradation in aqueous solution, primarily at the 8 position amino acid (Asn) and that the main hydrolytic reactions represent rearrangement of the amino acid (Asp) at the 3 position, cleavage of the bond between the 3 and 4 amino acids (Asp and Ala), and deamination and rearrangement of the Asn amino acid at position 8. The application also points out that commercially available hGRF in lyophilized formulations is stabilized with mannitol.

In combination, these three references as well as the background of the invention teach that GRF requires stabilization, that mannitol has been found suitable and what needs to be protected is either the methionine at position 27, the Asn at position 8, the Asp at position 3 and the bond between the Asp and Ala positions 3-4. It is also indicated that finding a suitable stabilizer is fought with difficulties. There is no

teaching or suggestion in these references or in the application background suggesting the use of saccharose as a stabilizer.

To overcome this basic deficiency, the Office Action relies on the Samaritani reference and various assertions contained in the paragraph which begins in the middle of page 3 of the most recent Office Action. It is respectfully submitted that such reliance is misplaced.

The Samaritani reference is especially, and explicitly, limited to human growth hormone (HGH). However, GRF is very different from HGH. GRF is a small peptide existing in 44, 40 or 37 amino acid chain forms with the activity residing mainly in the first 29 amino residues. HGH, in contrast, is a linear polypeptide containing a chain of 191 amino acids and 2 interchange disulfide bridges. Samaritani teaches that saccharose can stabilize HGH but does not teach or suggest that it can stabilize any other protein. As pointed out above, what requires stabilization in GRF is Met at position 27, Asp at position 3, the Asp - Ala bond at connecting positions 3-4 and Asn at position 8. The record does not establish that HGH has these amino acids at these positions and, therefore, the fact that saccharose may stabilize HGH does not provide any basis to suggest it will stabilize GRF.

Faced with these deficiencies, the Office Action assert, without citing any factual basis, that saccharose is a known "protein" stabilizer in the art and is known in the art as a stabilizer/preservative in "pharmaceutical formulations". However, such broad and all encompassing statements about "proteins" and "pharmaceuticals" does not suggest use in connection with GRF. At the very best, these assertions teach that saccharose might possibly be a stabilizer for proteins and that possibility should be explored. That however, is application of an "obvious to try" standard which is improper.

Next the Office Action states that the specification does not teach that saccharose will specifically denature or destabilize GRF nor were references cited to demonstrate this. From this assertion, the conclusion is drawn that "there is no evidence that GRF would be expected to behave differently in saccharose [then in the absence of saccharose or in the presence of mannitol]." (Office Action page 3, line 12-15). If this assertion is accepted as valid, then the evidence which is in the record that saccharose acts in a different way than GRF or GRF plus mannitol establishes the patentability of the instant invention. In this connection, the Examiner's attention is respectfully invited to Tables 1 - 3 of the present application. In Tables 1-3, formulations 1 and 2 contain mannitol while formulation 3 contains saccharose. Table 2 shows that with mannitol (formulations 1-2), the pH increased over the 4 weeks of the study whereas the formulation containing saccharose did not increase from the initial value. Table 3 shows that the peptide purity of the mannitol containing compositions decreased by about 2% or more over the 4 weeks of the study whereas the saccharose containing formulation lost only 0.2% over the same period of time. These results show that the formulation containing saccharose presented a better stability profile when compared to formulations containing mannitol or mannitol/phosphate buffer. Mannitol is a known stabilizer for GRF and therefore the results achieved with mannitol present are necessarily better than those with native GRF. The fact that saccharose provided a stability which is better than mannitol stabilized GRF is clearly surprising and unexpected when viewed in light of the conclusion in the Office Action that native GRF or GRF plus mannitol would be expected to behave in the same manner as with saccharose. Accordingly, the claimed invention does have greater than the expected properties.

Finally, the Office Action there are no unexpected beneficial results or properties because saccharose is known in the art as a "preservative" and that the

stability results in the specification are not greater than those which would have been expected from the prior art "to an unobvious extent." However, as the Office Action also points out, saccharose would not be expected to provide stability results which differ from that of mannitol stabilized or native GRF. The data in the application shows that it does.

In light of all of the foregoing considerations, it is respectfully submitted that the rejections in the current Office Action should be withdrawn and that this application is now in condition to be allowed. Accordingly, the early issuance of a Notice of Allowance is respectfully solicited.

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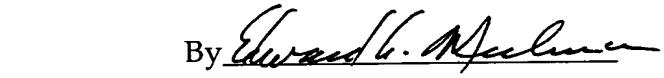
Respectfully submitted,

By 

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